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RECENT AND FORTHCOMING MEETINGS

11-14 April	WHO Expert Committee on Health Statistics : Subcommittee on Hospital Statistics, Geneva
11-15 April	WHO Expert Committee on Antibiotics, first session, Geneva
17-21 April	WHO Expert Group on Prematurity, Geneva
17-22 April	WHO Expert Committee on Rabies, first session, Geneva
18-21 April	WHO Expert Committee on Health Statistics, second session, Geneva
20-29 April	WHO Expert Committee on the Unification of Pharmacopoeias, sixth session, New York
May	WHO European Health Conference to consider the establishment of a Regional Office for Europe, tentatively Geneva
8 May	Third World Health Assembly, Geneva
30-31 May	Joint Committee on Health Policy, UNICEF/WHO, Geneva
1 June	WHO Executive Board, sixth session, Geneva
August	WHO Expert Group on School Health, Geneva
28 August-2 September	Joint ILO/WHO Committee on Occupational Hygiene, first session, Geneva
September	WHO Expert Committee on Tuberculosis, fifth session
September	WHO Committee for the Study of Chemotherapeutics in Tuberculosis
September	WHO Expert Committee on Venereal Infections : Subcommittee on Serology and Laboratory Aspects, second session, tentatively Paris
September	WHO Regional Committee for South-East Asia, third session, Colombo
4-7 September	WHO Regional Committee for the Eastern Mediterranean, third session, Istanbul
8 September	WHO Regional Conference on Statistics, Istanbul
11-16 September	WHO Expert Committee on Mental Health, second session, Paris
October, tentatively	WHO Expert Committee on International Epidemiology and Quarantine, third session, Geneva
9-14 October	WHO Regional Committee for the Americas, second session ; Pan American Sanitary Organization Directing Council, fourth meeting ; Ciudad Trujillo

INCREASING PRODUCTION OF ANTIBIOTICS

First session of the Expert Committee on Antibiotics

Antibiotics do not represent merely a momentary or transient phase in the history of therapeutics. Every day the results of current research show how great are the possibilities of treatment with antibiotics and justify the international interest at present being taken in their production. Six antibiotics—penicillin, streptomycin, chloromycetin, aureomycin, tyrothricin and bacitracin—are already being produced on a commercial scale in a number of countries.

Since penicillin first became widely used, for example, in programmes for the control of venereal diseases, many countries have experienced great difficulty in obtaining it in the quantities required for the general application of this therapy. It has, therefore, been found necessary to stimulate production of the more important new antibiotics on a national scale.

The First World Health Assembly recognized that

" the immediate object of WHO in this field should be to make technical knowledge on penicillin production available to countries contemplating the erection of plants ; to facilitate procurement of penicillin for countries unable to obtain this and similar drugs." [1]

Since then, efforts have been made to put into production the penicillin plants supplied by UNRRA to certain countries.[2]

Difficulties to be Overcome

The Expert Committee on Antibiotics, which held its first session in Geneva from 11 to 15 April 1950,[3] studied ways and means of giving assistance to countries requiring it in connexion with the drawing-up of plans and the installation and operation of antibiotic plants. The com-

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[1] *Off. Rec. World Hlth Org.* 18, 164

[2] *Chron. World Hlth Org.* 1949, 3, 53

[3] The following were present at this meeting :

Members :

Professor E. B. Chain, Professor of Biochemistry, Istituto Superiore di Sanità, Rome, Italy (*Chairman*)
Professor R. V. Christie, Professor of Medicine, University of London ; St. Bartholomew's Hospital, London, United Kingdom (*Rapporteur*)
Professeur M.-M. Janot, Professeur à la Faculté de Pharmacie de l'Université de Paris, France (*Vice-Chairman*)
Professor H. Theorell, Professor of Biochemistry ; Director, Section of Biochemistry, Nobel Institute of Medicine, Stockholm, Sweden
Professor S. A. Waksman, Chairman, Department of Microbiology, Rutgers University, New Brunswick, N.J., USA

Secretary :

Dr Mélanie Craipeau, Co-ordination of Research Section, WHO

The report of the committee will be published in the *World Health Organization : Technical Report Series.*

mittee analysed the difficulties encountered in this respect in certain countries and found that they were threefold :

(*a*) difficulty in obtaining plans or blueprints ;

(*b*) difficulty in procuring the necessary equipment ;

(*c*) lack of trained personnel to operate the plants efficiently.

With regard to the first point, the committee recognized that governments are obviously free to purchase plans from private firms either in Europe or in the USA, but it recommended that WHO, in collaboration with the United Nations and its other specialized agencies, should assist countries which, for financial reasons, are unable to obtain plans in this way.

FIG. 1. EXPERT COMMITTEE ON ANTIBIOTICS, FIRST SESSION

Left to right (seated round table) : Professor S. A. Waksman ; Professeur M.-M. Janot (Vice-Chairman) ; Professor R. V. Christie (Rapporteur) ; Dr S. S. Sokhey (Assistant Director-General, WHO) ; Professor E. B. Chain (Chairman) ; Dr Mélanie Craipeau (WHO) ; Professor H. Theorell ; Mme Y. Bezoari (WHO)

With regard to the second difficulty, the committee stressed that certain items of equipment—at present manufactured in only a very small number of countries—are essential for the efficient production of antibiotics. Such items include Podbielniak extractors for the production of penicillin, and special stainless-steel equipment for use in the preparation of streptomycin. In the course of the discussions, the committee considered the risk entailed in the possible use of the extractors for military purposes ; it was unanimously agreed, however, that, in the present state of knowledge, the extractors could not be used for such purposes. The committee therefore recommended that WHO should do everything possible to assist Member States to procure suitable equipment.

Adequate equipment is, of course, necessary, but it cannot be considered the only indispensable factor. It would be useless to install plants in countries which do not have the personnel to operate them. The lack of highly trained personnel remains the most serious obstacle to the production of antibiotics in several countries. The committee considered that the training of competent personnel is the most important factor in the production problem, and devoted much time to a consideration of this subject.

Technical Training in Antibiotics

The production of antibiotics is a complex process involving various methods of microbiology, chemistry, and pharmacology, and a new branch of engineering known as microbiological engineering. Such extensive knowledge can only be acquired by teams of research workers and technicians who are already well acquainted with the fundamental principles of these various branches of science. At present, most universities are unable to provide the comprehensive training required for such highly specialized work. Some provision should therefore be made for the training of specialists in centres which are devoted particularly to research and to study of the technique of antibiotic production.

The committee examined the various possibilities offered by official institutes in Europe and in the USA and recommended that WHO should approach those institutions in various countries which could provide facilities for the training of specialists on an international scale and, in particular, for the training of WHO Fellows. From this point of view, the Istituto Superiore di Sanità, Rome, which has a pilot-plant, offers particularly favourable conditions. This institute has experimental, semi-scale, and full-scale equipment for all stages in the manufacture of penicillin; this equipment includes fermentation vats with capacities ranging from 50 to 18,000 litres. Microbiological research is carried out along with pharmacological research. The institute will be able to accommodate 14 research workers each year to specialize either in biochemistry and microbiology, or in microbiological engineering. The Department of Microbiology of Rutgers University, New Brunswick, N.J., USA., could also this year take a few students specializing in microbiology. WHO will negotiate with other institutes in Europe and in the USA on the same subject.

The committee particularly emphasized that such specialist training in antibiotics should be given in centres where the atmosphere is conducive to research. The science of antibiotics is in the process of evolution, and new substances will probably still be discovered. Persons intending to specialize in this subject should not only become thoroughly versed in one particular method of antibiotic production, but should also acquire the

general knowledge which will enable them to follow the developments in this branch of science and, possibly, to make contributions of their own. On their return to their respective countries, the specialists thus trained would be able to install plants, thus obviating the main difficulties which have so far faced their governments. The committee therefore recommended that WHO should allocate fellowships for the training of specialists who, during their training, could take part in research and acquire the most up-to-date knowledge on the production of antibiotics.

* * *

Some apprehension was expressed regarding the financial risks which governments would have to face in installing plants whose equipment might soon become obsolete. The committee did not consider that the risk involved would be very great because the equipment required for the preparation of the antibiotics known at present could subsequently be used for the production of any others which might be discovered. Such fears should not prevent governments from immediately taking steps to install such equipment.

Research on Treatment with Antibiotics

Countries where antibiotics are available only in small quantities have a certain advantage. They, more easily than others, can group patients for treatment in a small number of centres, where antibiotic therapy can be applied under controlled conditions and where the results can be compared with those obtained with other drugs and, also, in untreated control-groups.

The committee suggested that such clinical research should be undertaken, under the auspices of WHO, in areas where antibiotics of proved value are in short supply. Such an experiment would have the added advantage of arousing interest in the use and production of antibiotics in countries where they are as yet little known.

A list should be drawn up of centres with adequate laboratories and qualified personnel—trained, perhaps, by means of fellowships. It must be ascertained that the number of patients is sufficient for the results of treatment to be statistically significant. Various institutions, the national medical councils, and some of the WHO expert committees, such as those on tuberculosis and venereal infections, should be asked for suggestions concerning the practical application of these projects.

Type-Culture Collections

There is an urgent need for improving the existing system of obtaining type-cultures capable of producing antibiotics. With the development of production there will be an increasing demand for collections of type-

cultures whose properties are kept constant and whose antibiotic-producing capacity is duly controlled. Existing centres responsible for type-culture collections should be approached. The committee recommended that WHO should ask these centres whether they would be willing to serve as official centres for the collection and distribution of certain strains of antibiotic-producing organisms, and of antibiotic-sensitive cultures for testing antibiotic activity.

Abstracts

The enormous number of scientific publications dealing with antibiotics is such that it is practically impossible for workers in this subject to keep abreast of them all. The committee therefore recommended that the Director-General should ask the Co-ordinating Committee on Abstracting and Indexing in the Medical and Biological Sciences to examine the most effective means of establishing a rapid and comprehensive abstracting service for antibiotics ; the abstracts in question should be issued in the form of separate fascicles.

Symposium and Congress

The committee discussed the advisability of organizing, in 1951, a symposium at which certain aspects of the problem of antibiotics would be discussed and, in 1952, a general congress on antibiotics. It recommended that these two proposals should be submitted to the Council for the Co-ordination of International Congresses of Medical Sciences.

STREPTOMYCIN AND TUBERCULOSIS

Experts from ten countries [1] met in Paris in February 1950, under the auspices of the United Nations International Children's Emergency Fund (UNICEF) and WHO, to compare results obtained in the treatment of tuberculous meningitis by streptomycin. Reports were submitted, particularly by countries in which there are streptomycin treatment centres and which receive supplies of streptomycin from UNICEF.[2] Various topics were discussed, such as the diagnosis of tuberculous meningitis, the routes by which antibiotics may be introduced into the meningeal spaces, posology, neurosurgical operations, examination of the cerebrospinal fluid, the concentration of streptomycin in the body fluids, electroencephalography,

[1] For list of experts attending the meeting, see page 166

[2] *Chron. World Hlth Org.* 1949, 3, 281

accidents due to streptomycin, and treatment with combinations of drugs. All of this work showed that important results had been achieved which permitted a deeper understanding of streptomycin therapy and, at the same time, raised new questions.

A working party dealt particularly with the implementation of the programme outlined jointly by UNICEF and WHO. It recommended that streptomycin should be reserved for the treatment of tuberculous meningitis, miliary tuberculosis, and primary infections when generalization may be imminent ; the treatment of other forms of tuberculosis in children which are amenable to this therapy could, however, be considered in case of necessity.

It would be desirable to establish streptomycin subcentres to make this treatment available to a greater number of cases. But care must be taken to keep the standard of treatment high and to have it administered by specialized personnel. In this connexion the working party urged governments to avail themselves of the offer of fellowships for the training of specialists in streptomycin therapy. Close collaboration should be established between the centres in each country and between those in different countries.

Some of the recommendations concern the work of responsible staff in the streptomycin centres themselves :

Variations in the potency and toxicity of streptomycin have been noted. Such variations should be reported without delay, together with details useful in the study of this problem.

A need for a uniform method of recording results has been felt. In addition, the centres should submit quarterly reports indicating the total number of cases treated, the number of children under treatment at the beginning and at the end of the period under consideration, the number of those who began or who finished treatment during this period, and the number of deaths recorded. An individual form for each case treated was proposed.

The working party expressed the desire that the countries who receive streptomycin through UNICEF should adhere to the standards established with regard to diagnosis and treatment. It adopted general recommendations for the current treatment of tuberculous meningitis in children and concerning its detection at an early stage ; it recommended the combined use of streptomycin and other antibiotics.

EXPERTS ATTENDING THE STREPTOMYCIN MEETING

Professeur E. Bernard, Paris, France
Professeur M. Bernheim, Lyons, France
Dr A. Breton, Lille, France
Professeur J. Chaptal, Montpellier, France
Professor C. Choremis, Athens, Greece
Professor C. Cocchi, Florence, Italy

Professor G. Daddi, Rome, Italy
Dr M. Daniels, London, United Kingdom
Professeur R. Debré, Paris, France
Professeur R. Du Bois, Brussels, Belgium
Professor D. S. Eleftheriou, Athens, Greece
Dr G. Fanconi, Zürich, Switzerland
Dr J. Fouquet, Paris, France
Professeur P. Giraud, Marseilles, France
Dr J. Houstek, Prague, Czechoslovakia
Dr Edith Lincoln, New York City, USA
Professor E. Lorenz, Graz, Austria
Dr A. Monbrun, Paris, France
Dr P. Mozziconacci, Paris, France
Dr R. Neubauer, Belgrade, Yugoslavia
Dr O. Ruziczka, Vienna, Austria
Dr Honor Smith, Oxford, United Kingdom
Dr K. Todorović, Belgrade, Yugoslavia
Dr I. Vanaanen, Rovaniemi, Finland
Dr O. Wasz-Höckert, Helsinki, Finland
Dr A. Ylppö, Helsinki, Finland

INTERNATIONAL COMPARABILITY OF HOSPITAL STATISTICS

Mortality statistics are a valuable source of information, but they give only an incomplete picture of the health conditions of a population ; an accurate picture requires statistics on both fatal and non-fatal types of illness. Interest in the methodical preparation of morbidity statistics goes as far back as the middle of the last century. However, progress in this field has been very slow, hampered as it was—among other factors—by the absence of a suitable list for classifying diseases. The recent adoption by WHO of an international classification covering both diseases and causes of death will permit full use of the ever-increasing volume of morbidity data.

Complexity of the Problem of Morbidity Statistics

Before any statistical classification can be applied to basic data, fundamental concepts must be defined and rules for the preparation of statistics formulated.

Although classification methods for mortality data are based on long experience, the systematic compilation of morbidity statistics is of fairly recent date. Moreover, the question of morbidity statistics is much more complex than that of mortality statistics. In the case of multiple causes of death, it has been decided to select the underlying cause for primary tabulations ; in multiple morbidity, one or the other cause might be of special interest depending on the type of information desired. Furthermore, in mortality statistics the underlying cause is selected irrespective of other stages in the development of the morbidity process prior to death ; in morbidity statistics, the interest is concentrated mainly on the phase of the disease process which is responsible for the period of illness.

The *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death* [1] sums up as follows the complex problem of morbidity data :

> Morbidity is far less definite than mortality, and represents a dynamic rather than a static phenomenon. The occurrence of death is a definite event, and the number of such events can be counted. An illness, on the other hand, varies from a minor deviation from normal health, which does not interfere with the performance of regular duties or activities, to the chronic case which calls for bedside or custodial care for an indefinite period. Furthermore, an individual afflicted with a disease may experience only one period of illness during the interval of observation, or may have repeated illnesses from the same disease. In addition, during the same period of illness, an individual may suffer from two or more distinct diseases. Thus, the basic problem as to what is to be counted becomes very complex, and it can be easily seen that the application of the present classification to morbidity statistics cannot be laid down as precisely and relatively simply as in mortality. The application will vary, depending on the kind of morbidity experience to be studied and on the purposes to be served by the statistics.

Unification of Hospital Statistics

" Hospitalized illness " represents that part of the total morbidity in the general population which receives hospital care ; it is the admission for hospital services and treatment which defines hospitalized illness. Thus its concept is free from the uncertainty in defining illness in general which is due to the difficulties of obtaining a clear-cut distinction between illness and health. However, relatively simple though this concept may be, many methodological aspects involved in general morbidity statistics are also common to hospital statistics.

There are at least three basic statistical groups to be considered in hospital morbidity statistics, i.e., hospitalized individuals (whether for the first time or not), number of admissions, and number of different morbid conditions comprising the total hospital morbidity. An individual may be admitted to a hospital one or more times during a certain period, and his case may give rise to one or more diagnoses counted in the total hospital morbidity. In cases of multiple morbidity, there may be a condition which describes best the necessity for hospitalization and which constitutes the index case in the patient's hospital record ; other conditions may be either independent of this cause or related to it. A patient repeatedly admitted to a hospital during a certain period may have each time a different illness or may be hospitalized repeatedly for the same morbid condition. Consequently, hospitalized illness may be analysed as a " person " concept in terms of individuals, or as a " patient " concept in terms of admissions. In the first case, persons admitted several times may be studied from the

[1] *Bull. World Hlth Org. Suppl. 1*, 1948, 1, p. xxxv and xxxvi

standpoint of determining whether the repeated hospitalization is due to the same or to different complaints. Hospital morbidity can also be examined in terms of the condition which brought the patient to the hospital, or in terms of total morbidity. In the latter case, multiple morbidity must be qualified as to the relationship to the principal diagnosis in order to allow an unduplicated count of morbid entities.

The principal and contributory diagnoses present another thorny problem to the statistician. Medical records often contain several diagnoses. All the conditions in a case of multiple morbidity may have contributed to the necessity for hospitalization. However, there can be selected a principal diagnosis which is a major factor in the illness and responsible for hospitalization ; the other diagnoses are contributory, whether they are related to the principal diagnosis or not.

The *Manual for Coding Causes of Illness* (US Public Health Service Miscellaneous Publication No. 32, Washington, 1944) defines the principal diagnosis as " the one which was chiefly responsible for the period of hospitalization, i.e., the one that led the patient to seek hospital care ". This *Manual* also gives descriptive details for multiple morbidity in terms of principal and contributory diagnoses.

The standard form used in the national morbidity survey in England and Wales provides another example of diagnosis classification. The general definition of the principal diagnosis as applied in England and Wales is, in its broad outlines, similar to that given in the US Public Health Service *Manual*. Also, the specific examples as to type of principal diagnosis supplied in the *Manual*, under rules for selecting the principal diagnosis, are in alignment with the specifications in the English classification system.

However, there is one marked difference between these two systems in the application of the general definition in the case of a disease complex with an underlying and a secondary condition. In the USA, a complication existing before admission may appear as the principal diagnosis for this particular hospitalization, e.g., a brain abscess resulting from bronchiectasis will be entered as the principal diagnosis, bronchiectasis being entered as a contributory condition. In England and Wales, the underlying condition always determines the principal diagnosis regardless of whether the complication supervened before admission to the hospital. Which of these two practices should be given preference ? A complication, especially if serious, will determine the need for hospitalization more accurately than the underlying condition which, in the absence of complications, might not perhaps require hospitalization. On the other hand, it can be argued that in complicated morbidity both conditions will require medical care and that the order of their registration is of little importance. Furthermore, if it is the underlying cause which is used as the principal diagnosis in cases of repeated admission, irrespective of the appearance of complications, it will serve to

indicate the persistence of the basic morbidity process and thus prove useful for certain types of study.

An Expert Subcommittee on Hospital Statistics was set up by WHO to deal with these problems and others involved in hospital statistics. This subcommittee held its first session in Geneva from 11 to 14 April 1950 [2] and submitted its report to the Expert Committee on Health Statistics, which approved it with the addition of a few comments.

In its study of the procedures for recording principal and accessory diagnoses, the subcommittee recognized that the choice between the American and the English practices should depend on which would be more profitable in the long run. It decided to recommend the method used at present in England and Wales, with the addition that notation should be made as to whether a complication is present when the patient is admitted to the hospital. Following acceptance of this proposal by the Third World Health Assembly, States will be required to supply the following information regarding diagnoses :

I. Principal disease, injury, or other condition which led to admission to a hospital ;

II. Principal complication(s) of I (stating the most important one first and indicating whether present at admission) ;

III. Principal accessory acute condition (stating whether present at admission) ;

IV. Principal accessory chronic condition.

The underlying cause should be entered in I if a complication in II was also present at admission, even though the admission was due to that complication ; and, in tabulation of statistics according to the principal cause of admission, common combinations of an underlying cause with complication should be distinguished.

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[2] The following were present at this meeting :

Members :

Dr E. L. Crosby, Director, Johns Hopkins Hospital, Baltimore, Md., USA
Dr Marie Lindhardt, Head, Statistical Section, National Health Service of Denmark, Copenhagen, Denmark (*Chairman*)
Professor J. Rasuhin, Professor of Social Medicine, University of Zagreb, Yugoslavia
Dr P. Stocks, Chief Medical Statistician, General Register Office of England and Wales, London, United Kingdom (Member of WHO Expert Committee on Health Statistics)

Observer :

Dr M. de Viado, Social Security Section, ILO

Secretariat :

Dr M. Pascua, Deputy Director, Division of Health Statistics, WHO (*Secretary*)
Dr Marie Cakrtova, International Nomenclature of Diseases and Causes of Death Section, WHO

Dr P. Foltz, Medical Director, Ospedale San Giovanni di Torino, Turin, Italy, was unable to attend.

The report of the subcommittee will be published in the *World Health Organization : Technical Report Series*.

Other Problems

It was decided that the section of the hospital record relating to identifying data should be recorded by medical record or registration officers and should include, as a minimum : name, type, and location of the hospital; the patient's name, national identity number (if any), hospital registration number, race, sex, date of birth, date of admission and of discharge ; and referral service (physician, other hospital, etc.).

The subcommittee also emphasized that provision should be made in the compilation of hospital statistics for counting the number of patients, admissions and discharges, and principal diagnoses of various kinds. It recognized the necessity for uniform definitions of the following terms : hospital, hospital bed, inpatient, outpatient, admission, discharge, patient-day, duration of stay, etc. ; but these definitions could not be thoroughly studied at the first session and will probably be placed on the agenda of a subsequent meeting.

Other questions of practical importance had to be postponed or entrusted to national health-administrations or national committees on health statistics. For example, the subcommittee thought it desirable to prepare statistics in certain hospitals for the mentally ill. Such studies, entrusted to national committees on health statistics, would give information concerning the origin of disorders involving hospitalization, according to the sex of patients, their age, civil status, occupation, duration of the illness, family history, and other measurable etiological factors. It is also desirable to compile statistics concerning the immediate result of hospitalization ; as far as possible, these should be supplemented by studies of sample groups of population in order to determine the prevalence of mental disorders.

The subcommittee unanimously acknowledged that, in general, the *Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death* meets the requirements of hospitals better than any other classification ; it therefore recommended its general use for preparing statistics on hospitalized illness. In the opinion of the subcommittee, it is not necessary that such statistics be prepared routinely in all countries for all hospitals ; it would suffice to encourage their compilation in a few countries or in certain given regions in which the population exposed to risk of disease can be defined, or, wherever such definition is not possible, in certain hospitals.

IMPROVEMENT OF STATISTICS ON FOETAL MORTALITY

Statistics for the city of New York show that, in 1948, 67% of the foetal deaths recorded occurred before the 20th week of gestation, 12% between the 20th and 28th weeks, and 18% after the 28th week (the period of gestation was not recorded for 3% of the deaths). What is the international significance of these figures ? Only after comparison with similar data from other cities and States can an answer be supplied to this question. Such comparison is rendered difficult, if not impossible, by the varying meanings attributed to the terms "stillborn" and "abortion". Thus, the New York statistician who considers as "stillborn" a foetus whose death occurred after the 20th week of gestation finds that almost one-third of the total number of foetal deaths comes into this category ; on the other hand, for the statistician of some other American State, who accepts the definition suggested by the League of Nations, according to which only foetal deaths after the 28th week are considered "stillborn", the category would include only 20% of the foetal deaths recorded.

The US National Committee on Vital and Health Statistics, which has recently been comparing stillbirth statistics for New York with those for other large towns in the USA, was "impressed by the magnitude of the foetal wastage problem as shown by the data for New York City, and that current data on stillbirths in the United States did not begin to indicate the true picture of such wastage". The committee stressed the gravity of this problem and, in its report to WHO, expressed the belief that even in New York City a very large number of foetal deaths was not registered. "If the 1948 New York City foetal death ratio, corrected for under-reporting, were applied to the US live birth data, there would be approximately 500,000 foetal deaths in the United States each year. The committee believes this is a public-health problem of great significance, the magnitude of which is not indicated by the current reporting of only 75,000 to 80,000 stillbirths in the United States."

At present, both the registration and the classification of this demographic data leave much to be desired. Valuable information is lost for want of some universally acceptable criteria which would allow research workers in various countries to use and interpret the statistics available.

Towards a New Terminology

The World Health Organization has set up a subcommittee for the definition of stillbirth and abortion, reporting to the Expert Committee on Health Statistics, to formulate a new demographic terminology which might be acceptable to all Member States. The problem which faced

this subcommittee, when it met in Paris from 27 February to 3 March,[1] was not a new one. A similar committee had been set up by the Health Organization of the League of Nations to give an appropriate definition of stillbirth, in the hope that all countries, or at least a large number of them, might adopt such a definition. In 1925, the following definition was proposed :

> A stillbirth is the birth of a (viable) foetus after at least 28 weeks of pregnancy, in which pulmonary respiration does not occur ; such foetus may die either (*a*) before, (*b*) during, or (*c*) after birth, but before it has breathed.

This definition was not welcomed as had been hoped ; although adopted by some countries, the majority rejected it. Consequently, little progress was made in this aspect of vital statistics, and there is considerable confusion with regard to terminology even now.

In a recent number of the *Epidemiological and Vital Statistics Report*,[2] Dr M. Pascua, Deputy Director, WHO Division of Health Statistics, surveyed the varying definitions of stillbirth accepted in various countries. He also pointed out some of the statistical repercussions of this situation and proposed some practical methods for helping public-health officers and other persons concerned with population trends to calculate more accurate demographic rates than can be obtained by the methods normally employed. There can be no radical improvement in vital statistics, however, until certain uniform standards and definitions, at present lacking, are adopted.

The failure of the attempt made by the Health Organization of the League of Nations to arrive at a universally acceptable definition of stillbirth shows the difficulties inherent in such an undertaking. It should not be forgotten that, for the jurist as well as for the statistician, there is an essential difference between a " stillborn child " and the product of " abortion ". The large number of provisions regarding the inhumation or the disposal of the dead foetus represents one of the factors which have induced the various countries not to require the registration of all foetal deaths, including those occurring in the early months of gestation.

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[1] The following were present at this meeting :

Members :

Dr D. Baird, Regius Professor of Midwifery, University of Aberdeen, United Kingdom (*Chairman*)
Dr M. A. van Bouwdijk Bastiaanse, Professor of Obstetrics and Gynaecology, University of Amsterdam, Netherlands
Dr F. F. Daily, Director, Division of Health Services, US Children's Bureau, Social Security Administration, Washington, D.C., USA (*Rapporteur*)
Dr L. Dérobert, Professeur agrégé à la Faculté de Médecine de l'Université de Paris, France
F. Fraser Harris, Director, Health and Welfare Division, Dominion Bureau of Statistics, Ottawa, Canada
Dr P. Stocks, Chief Medical Statistician, General Register Office of England and Wales, London, United Kingdom (Member of WHO Expert Committee on Health Statistics)

Secretary :

Dr M. Pascua, Deputy Director, Division of Health Statistics, WHO

The report of the subcommittee will be published in the *World Health Organization : Technical Report Series.*

[2] *Epidem. vital Stat. Rep.* 1948, **1**, 210

Taking all these factors into consideration, the subcommittee thought it preferable to formulate new definitions rather than to encourage acceptance of those attempted by the Health Organization of the League of Nations.

New Definitions

First to be studied was the term " live birth ", which is interpreted differently in different countries. Since the French language has no equivalent for the term " live birth ", the subcommittee prepared a definition which could apply equally to " live birth " and " live born " :

> Live birth is the complete expulsion or extracting from its mother of a product of conception, irrespective of the duration of pregnancy, which, after such separation, breathes or shows any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles, whether or not the umbilical cord has been cut or the placenta is attached ; each product of such a birth is considered live born.

Foetal death was defined as follows :

> Foetal death is death prior to the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy ; the death is indicated by the fact that after such separation, the foetus does not breathe or show any other evidence of life such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles.

These definitions were adopted by the Expert Committee on Health Statistics, which met in Geneva in April 1950. The Third World Health Assembly has now to approve them before WHO Member States actually adopt them.

When the recommendations of the Subcommittee on the Definition of Stillbirth and Abortion have been universally accepted, each country will, in the future, be called upon to prepare statistical tables of " live births " and " foetal deaths " for comparable periods of gestation. The subcommittee set these periods after studying the current data on foetal deaths and live births in various countries. It noted that very rarely are infants reported as being " live born " prior to the 20th week of gestation. On the other hand, there are recorded, in England, approximately three times as many live births as there are foetal deaths after the 28th week of gestation. It would therefore appear that a foetus begins to have a fair chance of survival at about this period. The subcommittee consequently decided that dividing lines at the 20th and 28th weeks could reasonably be used in the preparation of vital statistics, since clinical conditions affecting live birth and foetal death change appreciably at about these times.

On recommendation of the subcommittee, all countries are to submit tables of statistics covering all births, whatever the duration of gestation.

The data should be classified in four groups, as follows (duration of gestation being measured from the beginning of the last menstruation) :

Group I — less than 20 complete weeks of gestation ;

Group II — 20 complete weeks of gestation, but less than 28 ;

Group III — 28 complete weeks of gestation, or more ;

Group IV — gestation period not classifiable in groups I, II, and III.

With requisite changes of detail, the same classification should be used in the preparation of tables on " foetal deaths ". Groups I, II, and III may be described, respectively, as " early ", " intermediate ", and " late " foetal deaths. The terms " abortion " and " stillbirth " should be retained only if essential for use within a nation, and " stillbirth " only in so far as it corresponds to Group III (late foetal deaths). The subcommittee did not attempt to define " abortion ".

It is hoped that statistical tables covering all foetal deaths will be published in the near future. Countries unable to publish such tables immediately should at least register data and prepare tables covering all foetal deaths occurring after the 28th week of gestation.

Advantages of the New Definitions

These proposals open up new perspectives to all those concerned with vital statistics. The new definitions which the subcommittee proposed depart considerably from that adopted by the Health Organization of the League of Nations. The 1925 definition relied essentially on observing pulmonary respiration in the foetus. A number of States found this unacceptable. Clinicians declared that they felt neither morally nor ethically justified in considering the foetus dead if any sign of life had been observed, such as movement of voluntary muscles, beating of the heart, or pulsation of the umbilical cord. In adopting the new definitions, the subcommittee interpreted the feeling of a majority which holds it essential that signs of life other than respiration be taken into account. Some physicians might, perhaps, be rather unwilling to draw up a birth and a death certificate in cases in which it is difficult to ascertain whether the foetus is born alive. Experience shows that this happens quite frequently, even today ; consequently, a large number of such cases are not registered. It is for this reason that the subcommittee was unanimous in stressing the importance of doing everything possible to secure the co-operation of physicians and all other persons responsible for the registration of births. It further recommended that only a "foetal death certificate", and not both a birth and a death certificate be required for such cases. It is, as yet, too early to draw up a standard form for such a certificate, even though uniformity is needed.

The new definitions made no radical change with regard to classification according to the period of gestation. The terms " stillbirth " and " abortion " will no longer be used in international tables, but in practice, as has been seen, individual countries may still continue to use them in their national statistics. The new terminology is undoubtedly more flexible and, at the same time, better adapted to the requirements of the various countries. It will enable States with highly organized services to draw up detailed tables ; at the same time, less advanced countries will at least be able to register and classify their basic data. The figures will be comparable and, as a result, clinical and, more especially, etiological knowledge will, in all probability, benefit considerably. It is hoped that, in the light of this knowledge, it will be possible to take more effective public-health measures to reduce the number of lives lost among premature infants.[3]

[3] Another WHO expert group has recently studied the measures to be taken in this field (see below).

PROBLEM OF PREMATURE INFANTS

WHO has given particular attention to the problem of prematurity, an important cause of infant mortality. A group of experts which met in Geneva from 17 to 21 April 1950 emphasized the necessity for organizing and encouraging appropriate action with regard to prematurity and for collecting data on the various aspects of the problem.[1]

Neonatal Mortality-Rate

The expert group stressed the importance of reducing the neonatal mortality-rate by giving special care to all infants weighing 5½ pounds (2,500 g.) or less, regardless of the length of the gestation period. A definition, established solely on birth weight, however, has the disadvantage

[1] The following were present at this meeting :

Members :

Dr L. Camacho, Chief, Maternal and Child Health Centre, Public Health Department, Quito, Ecuador
Dr V. Mary Crosse, Paediatrician, Birmingham Regional Hospital Board, Birmingham, United Kingdom
Professeur M. Lelong, Clinique de Puériculture de la Faculté de Médecine de l'Université de Paris, France
Dr S. Z. Levine, Professor of Paediatrics and Paediatrician-in-Chief, New York Hospital, Cornell Medical Center, New York City, N.Y., USA (*Chairman*)
Miss E. Magnussen, Director, Nursing Division, National Health Service of Denmark, Copenhagen, Denmark
Dr A. Ylppö, Professor of Paediatrics, University of Helsinki ; Chief, Children's Clinic, Helsinki, Finland (*Co-Chairman*)

Adviser :

Miss D. Batt, Matron, Training Centre for Plunket Nurses, Dunedin, New Zealand

Secretary :

Dr Ethel C. Dunham, Consultant, Maternal and Child Health Section, WHO

The report of the group will be published in the *World Health Organization : Technical Report Series.*

of being based on the assumption that the exact weight at birth will be known—information which cannot always be obtained. For this reason, and for the promotion of international uniformity, the expert group recommended the use by all countries of the definition which was adopted by the First World Health Assembly and which is set forth in the *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death* : [2]

> For the purpose of this classification an immature infant is a liveborn infant with a birth weight of 5½ pounds (2,500 grams) or less, or specified as immature. In some countries, however, this criterion will not be applicable. If weight is not specified, a liveborn infant with a period of gestation of less than 37 weeks or specified as " premature " may be considered as the equivalent of an immature infant for purposes of this classification.

The problem of prematurity should be approached in two ways : first, by planning to reduce the incidence of premature birth, and, secondly, by providing special care for premature infants. Preventive measures, since they are a part of prenatal care, may precede the development of special programmes for care of the infant.

Preventive Programme

Certain conditions are prerequisites for the carrying-out of a preventive programme. These conditions include : a well-organized public-health service with a section actively concerned with maternal and child health ; definite indications that the infant mortality-rate is declining ; and provision of facilities for hospitalization of pregnant women, particularly those with complications. In many instances, the cause of premature birth is not known, and studies of this problem are indicated. There are certain factors that are known to affect the incidence of premature births ; for example, early and continuous prenatal care, maintenance during pregnancy of good physical and mental health, services such as prenatal clinics providing medical, nursing, public-health and social services, hospitalization for women with complications, well-organized obstetric services, legislation for protection of mothers, etc., are preventive factors the importance of which should be stressed by an educational programme.

Care of Premature Infants

In carrying out a programme of special care for premature infants, there are also certain prerequisites. The entry on the birth certificate of the birth weight and the length of the gestation period (or at least one of these particulars) should be made compulsory. Exact statistics of foetal

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[2] *Bull. World Hlth Org. Suppl. 1*, 1948, 1, 212

and neonatal mortality must be available. It is essential that qualified medical and nursing services should be provided, as well as hospital services and facilities suitable for the care of premature infants.

The carrying-out of a programme of care of premature infants will differ according to whether confinements in a given region are in hospital or at home. The group suggested that either one or both of these programmes might be instituted as a demonstration, including the integration of all existing resources of the community into the programme. If a hospital centre for the care of premature infants is established, at least one paediatrician and nurse specially trained in the care necessary for such infants must

FIG. 2. EXPERT GROUP ON PREMATURITY

Left to right (seated round table) : Dr L. Verhoestraete (WHO) ; Miss E. Magnussen ; Dr V. Mary Crosse ; Miss D. Batt ; Dr Elinor Downs (WHO) ; Dr A. Ylppö (Co-Chairman) ; Dr S. Z. Levine (Chairman) ; Dr Ethel Dunham (WHO) ; Miss H. Martikainen (WHO) ; Dr L. Camacho ; Professeur M. Lelong

be in attendance. The instruction of the mother in premature infant care should be started while she is in the hospital and continued in the home.

Where nursing care is given to the infant at home, provision must be made for hospitalization in case the infant's condition calls for special care.

Provision should be made for transportation of the infant and for follow-up medical care.

Development of Programmes : Education : Research

Whether care be given in the home or in hospital, these initial programmes will be progressively extended to increasingly larger areas wherever possible. To achieve this, an administrative organization will be required to develop and carry out the programme.

In some regions a programme of education of physicians, nurses, and midwives in the care of premature infants must be instituted, while in others existing programmes may need to be expanded. Educational programmes should include, particularly, practical experience in a well-equipped hospital. In addition, there should be instruction in and demonstration of techniques of care and, later, refresher courses.

Research programmes suggested were studies to correlate the gestation period with birth weight and other criteria of prematurity ; nutrition of pregnant women and its relation to prematurity ; causes of premature birth ; and the relation of social and economic factors to the problem. Governments could give valuable assistance by granting scholarships for such research, as well as for a study of the highly specialized subject of prematurity and related topics.

FIRST RESULTS OF MASS VACCINATION WITH BCG

The object of the campaign for mass vaccination with BCG begun in 1948 by the Danish Red Cross, the Swedish Red Cross, and the Norwegian Relief for Europe, with material aid from the United Nations International Children's Emergency Fund (UNICEF) and technical help from WHO —known as the Joint Enterprise—is to test over 30,000,000 children and young adults with tuberculin and to vaccinate with BCG all non-reactors.[1]

This vast operation is at present being carried out in 17 countries. It provides a unique opportunity for beginning the study of several problems relating to tuberculosis on the basis of a sufficiently large number of observations to enable the results to be analysed statistically. Various questions relating to the epidemiology of tuberculosis—for example, variation in tuberculin-sensitivity according to districts, climate, race, age, and sex—vaccination and its effects, and the efficacy of tuberculin-tests may now be investigated practically with the aid of data obtained in widely different parts of the world. To examine and analyse this important collection of data a Tuberculosis Research Office was set up by WHO in Copenhagen.[2] The individual cards of tested and vaccinated individuals are sent to this office after being subjected to a preliminary analysis locally in certain cases. Since the beginning of the campaign, information has been received from various countries, particularly from European countries. This abundant information has provided Dr H. J. Ustvedt, Deputy Director of the

[1] *Chron. World Hlth Org.* 1948, **2**, 34
[2] *Chron. World Hlth Org.* 1949, **3**, 77

Joint Enterprise, with material for three important articles which appeared recently in the *Bulletin of the World Health Organization*.[3] These articles constitute the first contribution of the Joint Enterprise to the study of three problems : (*a*) technique of tuberculin-testing ; (*b*) local reaction in BCG vaccination ; and (*c*) tuberculous disease in BCG-vaccinated individuals.[4]

As Dr Ustvedt points out, mass-vaccination campaigns hardly lend themselves to strict scientific investigation. The time available is short ; the training of the medical and nursing staff responsible for carrying out the tests and reading the reactions varies ; the material inoculated is not always homogeneous ; children often fail to appear for re-examination ; and information concerning the previous morbidity records of the children is difficult to ascertain. In addition to these difficulties, there are biological factors, such as the different tuberculin-sensitivity in different areas, to consider, apart from individual variations which cannot always be taken into account. In view of these two groups of variable factors it is difficult to regard the present results as absolute. However, it is now possible to lay down various valuable practical rules, to define a number of problems requiring more thorough experimental investigation, to refute some of the arguments, scientific or " sentimental ", and perhaps to overcome certain prejudices.

Tuberculin-Testing

Pre-vaccination test

The pre-vaccination test with tuberculin is intended to select for vaccination individuals who are not yet infected with tubercle bacilli, and to exclude from vaccination allergic individuals in whom reinfection might have unpleasant consequences. There is at present, however, no method by which the infected can be distinguished with certainty from the non-infected. With each method it is possible that positive reactions will occur in non-infected individuals (non-specific reactions) or, on the other hand, that negative reactions will be observed in individuals who, in point of fact, are infected. It is necessary, therefore, to study various methods of tuberculin-testing and to choose that method which will disclose the highest proportion of infected persons, who should not be vaccinated, and the highest proportion of non-infected persons who should be vaccinated. The criteria for a positive reaction should be chosen so as to satisfy this dual requirement, and it can be readily understood that these criteria have been discussed at great length.

Instructions have been drawn up by the Joint Enterprise for the guidance of the personnel responsible for the various operations. These instructions

[3] *Bull. World Hlth Org.* 1950, **2**, 355, 441, 469

[4] These articles, together with a study on BCG culture (see page 187 of this number of the *Chronicle*), form a complete issue of the *Bulletin*.

define, in particular, the criteria for a positive reaction which are recognized by the Joint Enterprise. Moderately sensitive test-methods, which exclude tuberculous persons from vaccination and, as far as possible, satisfy the two conditions mentioned above, are to be used.

The tuberculin-test may be carried out in various ways, the principal methods being :

(*a*) application of tuberculin ointment under plaster (Moro patch-test) ;

(*b*) intracutaneous tuberculin injection (Mantoux test) with doses varying from 1 TU to 100 TU (1 TU = 0.01 mg.) ;

(*c*) Pirquet cutaneous test with addition of adrenalin to the tuberculin (AP test).

Instructions given by the Joint Enterprise to doctors and nursing staff provide for the application of the Moro patch-test to children up to 12 years of age. The comparison of this test with the Mantoux test with 1 TU or 10 TU was carried out on more than 24,000 individuals, mainly in Poland, examined by the Joint Enterprise, and the results showed that the sensitivity of the patch-test seems to correspond fairly closely to that of Mantoux 1 TU ; 95% of the individuals reacted to both tests. On the other hand, the patch-test is sometimes less sensitive than Mantoux 10 TU in the same age-group. It becomes less effective than Mantoux 1 TU or 10 TU as the age of the children increases, particularly after the age of 12 (see fig. 3). The possibility of non-specific reactions being elicited by the Mantoux test must be considered ; in the case of the children in question, however, such reactions are of no great importance.

The application of the Mantoux test to children over 12 years raises subsidiary questions. What dose of tuberculin should be employed— 1 TU, 3 TU, 5 TU, 10 TU, or 100 TU ? This is a complex question because, as has been pointed out, tuberculin-sensitivity varies in different districts, and all the factors affecting the reaction cannot be taken into account.

It was decided that, in the Joint Enterprise campaign, two successive tests should be made ; a dose of 1 TU was used for the first test and, if this was negative, a dose of 10 TU was used for the second. Other combinations, such as 3 TU and 33 TU, 5 TU and 50 TU, are still being investigated.

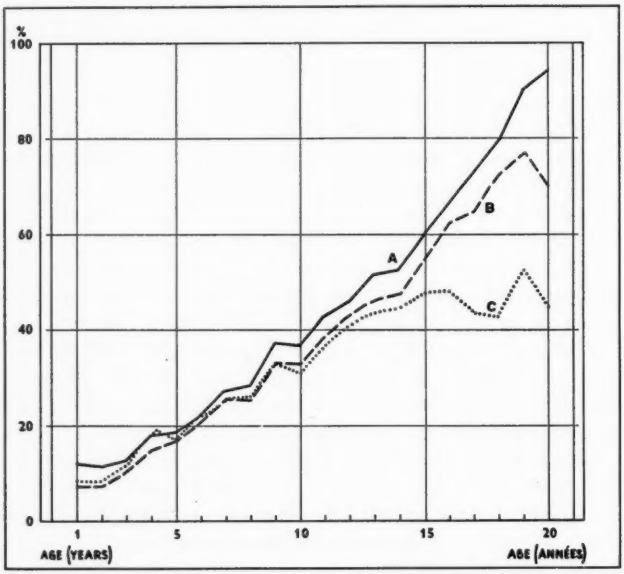
What are the criteria for a positive reaction ? Here again opinions differ. The extent, after a certain time interval, of the induration caused by the injection has been selected as a criterion, and a reaction which, after 72 hours, shows an induration of 3 mm. to 4 mm., or more, is said to be positive.

The AP test has not yet been generally used in the Joint Enterprise campaigns but, elsewhere, the results of tests on 23,000 children have shown

that it is as effective as Mantoux 10 TU and seems to produce fewer non-specific reactions. Mass-vaccination on the basis of a single negative AP test would appear to be justified, and its general employment should be considered.

The use of diluted BCG vaccine instead of tuberculin for the pre-vaccination test had been advocated in order to simplify the technical procedure by working with one test and one reagent. In this connexion, however, further studies are required.

FIG. 3. PERCENTAGE OF REACTORS TO TUBERCULIN ACCORDING TO AGE



Studies carried out on 12,448 males in Myslenice and Wadowice powiats, Poland, from May to June 1949

———— Mantoux 1 TU and 10 TU
- - - - - - - - Mantoux 1 TU
..... Moro patch-test

Post-vaccination test (control of vaccinated individuals)

The object of the post-vaccination test is to furnish information regarding the degree of tuberculin-sensitivity conferred by vaccination, such sensitivity being regarded as an index of immunity. This criterion is certainly not absolute, but cutaneous hypersensitivity to tuberculo-protein is the only criterion for the assessment of allergy, which is itself the only index of immunity obtainable for human beings. Cutaneous hypersensitivity is

merely one of the aspects of allergy ; it may decline or disappear, while the allergy of other organs still remains.

A specific tuberculin-reaction appearing after BCG vaccination in a non-reactor to the same test shortly before vaccination shows that the latter has " taken ". The connexion between this fact and the increased resistance of the individual is, however, not known. The results of about 30,000 post-vaccination reactions examined by the Joint Enterprise have been obtained from Czechoslovakia, Greece, Poland, and Yugoslavia. Most of the studies showed a very high proportion of positive reactions— in most cases, the percentage exceeded 90% and, in some cases, 99%-100% reactors were disclosed. These results are therefore entirely satisfactory from the practical point of view, although lower figures (70%) have been recorded in certain groups. It should be noted that post-vaccination tests should be carried out by the same methods as the pre-vaccination tests.

Local Reaction in BCG Vaccination

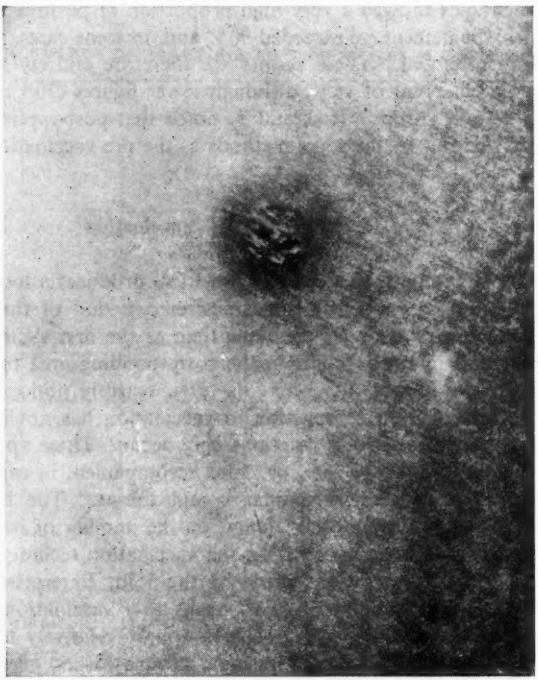
In healthy individuals, vaccination with BCG produces a local reaction at the site of inoculation which appears after a period of three to four weeks, or longer, i.e., at about the same time as the first signs of allergy can be detected. Enlarged glands in the corresponding area may also be observed. This " normal BCG-itis " is often scarcely noticeable to the individual. Nevertheless, the reaction to vaccination has not always this benign character. Strong local reactions may occur. These appear in the form of an induration of 10 mm. or more accompanied, in certain cases, by ulceration, pustules, and glandular complications. The intensity of the reaction depends, among other things, on the number of bacilli (killed or living) which have been injected, on the vaccination technique, and on individual factors. Observations made by the Joint Enterprise revealed, among 14,000 persons examined 6 to 10 weeks after vaccination, 3% reactions measuring 10 mm. or more. Ulcers appear relatively earlier, i.e., between the 4th and 8th weeks ; in some groups ulcers were observed in 0.23% of the individuals. " Local abscesses " are mentioned in some studies. Cases of glandular complications with suppuration are of the greatest practical importance. As many as 196 cases out of 62,200 individuals (0.03%) have been observed in certain countries ; the left axilla was affected in most of the cases.

If suppurating lymphadenitis, abscess formation at the site of vaccination, and local ulcers with diameters of 10 mm. or more are regarded as " complications ", the proportion of these phenomena observed in the Joint Enterprise campaigns is between 0.1% and 0.5%.

A special case of strong reaction is the " Koch phenomenon " or accelerated formation of the tuberculous nodule (see fig. 4). It occurs much

earlier than a normal reaction and appears in the form of erythema, pustules, and, sometimes, ulcers or necroses, and may be complicated by glandular reactions. It is the result of a reinfection and appears in individuals who, before vaccination, were already infected with tubercle bacilli. This phenomenon, which was described by Koch in his experiments on animals,

FIG. 4. KOCH PHENOMENON



Photograph submitted by Dr E. Graubner, Pilsen, Czechoslovakia

has been observed particularly during experiments on the treatment of tuberculosis with BCG and, in isolated cases, after BCG vaccination.

A curious case appears in the literature on the subject :

A girl was vaccinated with BCG on a negative Mantoux 100 TU. The post-vaccination test carried out three months later was positive. Three months after this last test she fell and injured her elbow ; the lesion was accidentally contaminated by sputum containing tubercle bacilli of the human type. The girl soon showed a tuberculous ulcer, and caseous lymphadenitis became apparent in the regional glands on the 27th day after inoculation.

Owing to the imperfections of tuberculin-tests and despite all the precautions adopted, it is impossible, during vaccination campaigns involving millions of individuals, entirely to avoid vaccinating persons infected with tubercle bacilli. The lowered tuberculin-sensitivity of individuals suffering from various other diseases may result in individuals who are really infected being recorded as non-infected. For this reason, and also owing to certain individual-sensitivity factors, Koch phenomena are liable to occur during mass vaccinations. The difficulty of defining the Koch phenomena exactly is one of the reasons why the statistical results on this subject are not very accurate. Nevertheless, it would appear from the various investigations that strongly marked Koch phenomena likely to prove disagreeable for vaccinated individuals are of extremely rare occurrence. Only 7 cases of ulceration were noted in a district where the percentage of tuberculin-reactors is very low. The studies carried out show that strong local reactions during the first week after vaccination seem to have occurred only very rarely in individuals who were vaccinated after giving a negative reaction to a patch-test, Mantoux 10 TU and 50 TU, and an AP test. This may be taken as an indirect proof of the fact that the technique adopted for the tuberculin-testing was fairly satisfactory, as far as selection of individuals for vaccination was concerned.

Tuberculous Disease in BCG-Vaccinated Individuals

Can BCG produce, activate, or aggravate a tuberculous infection ? The question has not been definitely settled. The problem has too often been approached on non-scientific lines and should be re-investigated with complete impartiality.

BCG has often been accused of causing tuberculous infection, reviving latent infection, or accelerating the crisis in active tuberculosis. Before discussing the question itself, Dr Ustvedt points out some of the misconceptions on the part of the public and the misunderstandings which are liable to occur during mass-vaccination campaigns : for example, a tuberculin-test may be mistaken for a BCG vaccination ; vaccination against smallpox or diphtheria may be confused with BCG-vaccination ; a non-tuberculous disease or normal BCG-itis may be diagnosed as tuberculosis, etc. It is certainly easy to rectify statements resulting from such mistakes and to dispose of unfounded judgements. That being done, some cases in which BCG might have played a part in the development of a tuberculous infection should be objectively examined.

Cases of tuberculosis have occurred in individuals vaccinated with BCG. The immunity conferred by the vaccine is admittedly not absolute. Can BCG, however, be held responsible for the infection ? Thorough investigation has shown that, since 1930, BCG has not caused progressive

tuberculosis in laboratory animals, that it has not been virulent in human beings, and that no fact has come to light which has caused the innocuousness of this vaccine to be questioned.

Individuals who are already infected with virulent bacilli but who did not react to the tuberculin-test may be vaccinated. It was stated earlier that these tests do not reveal all the infected persons. Cutaneous sensitivity may be greatly reduced in individuals who have previously suffered from tuberculosis and may decline or disappear during infectious diseases such as pertussis or measles. Moreover, the person may, at the time of vaccination, be in the pre-allergic phase of an infection caused by virulent tubercle bacilli and may not react to the tuberculin. The vaccination of such individuals—infected but non-reactors—may cause accidents and Koch phenomena which, if violent, are likely to influence the course of the infection.

In the Joint Enterprise campaigns, various individuals have been observed in whom the following symptoms appeared 10 to 12 weeks after vaccination : erythema nodosum, hilar adenitis, primary complex, and pleurisy. It is known that erythema nodosum may be provoked by various agents (for example, drugs and vaccines), and BCG may possibly have a similar effect. In a few cases of primary tuberculosis which occurred soon after vaccination, no causal relation could be established between the vaccination and the disease. To avoid controversy, however, persons who have suffered from tuberculosis should not be vaccinated, even if they have become negative to tuberculin. The same precaution should be taken when an epidemic of a childish complaint, which weakens the sensitivity to tuberculin, has broken out in an area.

The influence of BCG on active tuberculosis has already been the subject of much investigation. While some doctors felt that it had a certain beneficial effect, others considered that it might not always be harmless for patients suffering from active tuberculosis. When large doses of BCG are used, it must obviously be expected that such persons will show a reaction similar to that produced by tuberculin. After inoculation with strong doses of BCG, a focal reaction, a rise in temperature, the transient aggravation of pleurisy, and articular phenomena have been observed. While it cannot be said with certainty that these manifestations are a consequence of vaccination, the possibility cannot be denied absolutely. Some doubtful cases, in which it is not possible to determine precisely what part was played by BCG in the development of a non-apparent disease which sometimes proved fatal, are discussed in detail in the article by Dr Ustvedt. This author concludes by emphasizing that, in spite of the abundant documentary evidence asserting the harmlessness of BCG, vaccination of persons suffering from active tuberculosis should, as far as possible, be avoided. Improving the tuberculin-tests, thus making it possible to discriminate with increasing precision between infected and non-infected individuals, will be the surest means of attaining this end.

In the last part of this article, Dr Ustvedt reviews the various forms of tuberculosis observed in individuals vaccinated with BCG. Tuberculous meningitis and miliary tuberculosis have been observed in 21 children during the campaigns in various countries ; in most cases the date of appearance of the symptoms makes it likely that the vaccination was carried out during the pre-allergic phase. There is no evidence to show that BCG vaccination contributed to the development of the disease.

In his paper, the author points out that the isolation of human-type bacilli from a tuberculous individual is not in itself sufficient proof that BCG was not responsible for the disease. If BCG were to become virulent, it might possibly present some of the characteristics of human-type bacilli, especially with regard to its pathogenicity for certain experimental animals. Cases of erythema nodosum are very controversial since they can be of non-tuberculous origin. Cases of primary tuberculosis have been observed in persons infected with virulent bacilli shortly before or after BCG vaccination. However, when the first 6 to 8 weeks after vaccination have elapsed without any superinfection and when post-vaccination allergy has been obtained, the manifestations of primary tuberculosis disappear in a striking manner. This last phenomenon is characteristic and has been observed in most of the groups vaccinated with BCG.

BCG ON SAUTON'S MEDIUM

BCG is maintained at the Institut Pasteur in Paris by subculture of the strain every 15 days on Sauton potato. For the preparation of the vaccine itself, it is necessary to obtain a culture which gives a thick film. For this purpose, therefore, BCG is grown on Sauton's liquid medium, on which two passages only are carried out.

Earlier observations by Danish workers showed that the vitality of BCG was diminished when subcultured serially on Sauton's liquid medium : the cultures were less luxuriant than on potato and the allergizing power of the strain was reduced, but a passage from time to time on bile potato was enough to restore the original properties of the strain.

Van Deinse and Sénéchal have reconsidered this question in detail and have given their results in an article appearing in the latest number of the *Bulletin of the World Health Organization*.[1] These authors studied the behaviour of BCG in a long series of subcultures on Sauton's liquid medium alone. They noticed that, at the fourth passage, the growth of the culture began to slow down. Instead of a film covering the surface of the medium,

[1] Van Deinse, F. & Sénéchal, Françoise (1950) *Bull. World Hlth Org.* **2**, 347

dry granules were formed (see fig. 5). The size of the bacilli was also smaller by a quarter or a fifth than that of bacilli maintained on potato. This fact may be of considerable importance in the standardization of BCG vaccine, as the same weight of culture may contain a different number of

FIG. 5. EFFECT OF SAUTON'S MEDIUM ON THE BIOLOGICAL PROPERTIES OF BCG CULTURES

A B

A = normal culture
B = culture after 37th passage on Sauton's medium

bacilli according to the medium used. After about 20 passages on Sauton's medium, the ability of the strain to produce a local reaction in the guinea-pig is also reduced.

The Danish authors observed that a few passages on bile potato restored the vitality of the culture. Van Deinse and Sénéchal showed that the presence of bile was not essential and that a single passage on potato was enough to restore the normal development of the strain. They concluded—thus confirming the observations made by Guérin 25 years ago—that Sauton's liquid medium is unsuitable for the maintenance of BCG and that its use is to be discouraged.

WORLD DISTRIBUTION OF TRACHOMA

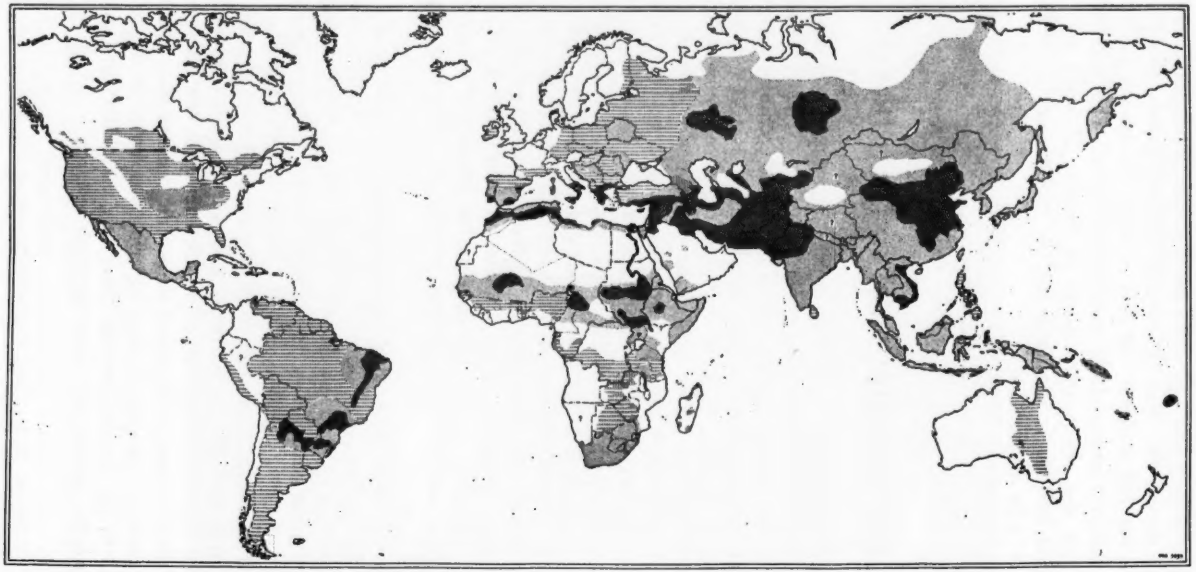
Before any action against trachoma can be undertaken, it is important to study its present distribution throughout the world. Spread over almost all continents, this disease is the cause of enormous economic losses. It afflicts a great number of people from childhood and is, to a considerable extent, chronic in nature. Its most serious consequence is blindness.

The Health Organization of the League of Nations was aware of the seriousness of the problem presented by trachoma and, between 1925 and 1935, made a number of studies of the geographical distribution of the disease. Since fourteen years had elapsed since the last of these studies was carried out, a joint OIHP/WHO study-group which met in Paris in October 1948 [1] " recommended that WHO obtain from governments up-to-date information on the prevalence of trachoma throughout the world, based on returns established after examination of schoolchildren, army recruits and samples of population, and on the percentage of trachoma cases to the total number of eye patients treated in ophthalmic hospitals and clinics ".

An article—" World distribution and prevalence of trachoma in recent years "—by Dr M. M. Sidky, formerly member of the WHO Epidemiological Studies Section, and Dr M. J. Freyche, Chief, WHO Epidemiological Information Section, was published in the November-December 1949 number of the *Epidemiological and Vital Statistics Report*.[2] This work is based on information which WHO has received from governments. As pointed out by the authors, the results of the survey are not yet complete since there are large areas from which no documentation has been sent to WHO, and since statistics with regard to chronic diseases must always be treated with caution. In spite of these imperfections, however, the conclusions reached by the authors provide some very useful data and may be used as a basis for further and more thorough research.

[1] *Off. Rec. World Hlth Org.* **19**, 27 ; *Chron. World Hlth Org.* 1948, **2**, 260
[2] *Epidem. vital Stat. Rep.* 1949, **2**, 230

FIG. 6. APPROXIMATE GEOGRAPHICAL DISTRIBUTION OF TRACHOMA



- evidence of present and past infection in majority of inhabitants
- very common
- not very common, or common in local areas
- rare, but present in a few foci
- absent
- ? no recent information

The following points, in particular, should be noted :

(1) The trachoma index for schoolchildren is lower than for the population as a whole. This observation is based on information furnished by several countries. In Albania, for instance, according to an inquiry made in 1944, the trachoma index for schoolchildren was 14%, whereas the total trachoma index was 27%.

(2) In countries where the disease is highly endemic, there may be zones which are relatively free from infection. In Iran, for example, the trachoma indices in certain endemic areas may be from 80% to 90%, while in other areas of the same country they may be from 2% to 10%.

(3) An important fact which merits particular attention is that regions which were, until the last few years, considered to be practically free from trachoma appear from recent surveys to be highly infected by the disease. In Tanganyika, for example, of a group of 4,000 recruits who were examined, 23% were found to be infected with trachoma ; and, in the higher regions in the south-west of the country, of 3,177 adults and children examined, 54% were suffering from the disease.

(4) On the other hand, in countries where trachoma previously existed, sanitary measures and the raising of the standard of hygiene among the people have led to the gradual disappearance of the disease. For example, only a few sporadic cases are found in Belgium, Denmark, Luxemburg, the Netherlands, Switzerland, and the United Kingdom. An analogous situation is noticed in other countries, in spite of chance outbreaks caused by the bringing in of infectious elements from the outside. This is the case in Austria, France, and the US Zone of occupied Germany. Recent statistics show, however, that the gradual decrease in trachoma is continuing ; and the results obtained from measures systematically applied in countries still affected, such as Ireland and the USA, indicate that trachoma will gradually disappear.

Notes and News

Anaesthesiology Training-Centre Established by WHO

Twenty-one WHO Fellows, coming from Austria, Denmark, Finland, Iceland, Norway, Sweden, and Yugoslavia, have arrived at the recently established anaesthesiology centre at Copenhagen to learn new techniques in this medical speciality. The centre, which opened 3 May 1950, has been established in collaboration with the Faculty of Medicine of the University of Copenhagen to assure training for anaesthesiologists, of which Europe has great need at the present time.

Graduate physicians will take a one-year course. The training centre will benefit from the experience of two eminent specialists, Dr S. G. Cullen, of the University of

Iowa, and Dr Ralph Waters, former Professor of Surgery and Anaesthesiology of the University of Wisconsin. A British specialist, Dr Phyllis Edwards, and several Danish physicians will assist in the teaching.

Serodiagnosis of Kala-azar

A simple method for the serodiagnosis of kala-azar has recently been tested by WHO specialists. The antimalaria demonstration team in East Pakistan has undertaken a campaign against kala-azar, in addition to its regular activities.[1] It has been noted during the operations that serological reactions to formalin and to antimony give entirely satisfactory results when they are performed by means of capillary tubes. The practical advantage of this method is obvious : the taking of the blood samples is infinitely easier than by venipuncture.

Filariasis in Ceylon

At the beginning of March, Dr M. O. P. Iyengar conducted a filariasis-control programme in the Galle Municipality, Ceylon. A previous survey of this region had revealed a high endemicity rate of filariasis due to *Wuchereria bancrofti* transmitted by *Culex fatigans*. The programme included treatment of breeding-places with larvicides and training of personnel in control measures. It was decided to treat the breeding-places weekly, to examine them two days after treatment, and, if necessary, to repeat the treatment. Attention was also given to the eradication of other sources of pullulation, such as certain plants, defects in septic tanks, and inadequate drainage systems.

BCG in Egypt

Dr D. R. Thomson, Regional Adviser for Tuberculosis, WHO Regional Office for the Eastern Mediterranean, has had several discussions with officials of the Ministry of Public Health of Egypt with a view to establishing an antituberculosis centre in that country. He has also conferred with Dr J. H. Holm, Director, Tuberculosis Division, Statens Seruminstitut, Copenhagen, and with the Egyptian authorities concerning BCG vaccination in Egypt. It has been decided to vaccinate the total population of certain provinces, concentrating all the available teams there. A BCG production centre will be set up at the Fouad Serum Institute at Agouzi.

Malaria

India

Investigation on the incidence of malaria has been proceeding in the Terai region in India.[2] Of 778 children examined in 28 villages, 548 were found with enlarged spleen ; of 187 blood smears examined from children under two years of age, 49% were positive for malarial parasites.

High incidence of malaria was also observed in similar studies in the Jeypore Hills area. It was noted that there is a general tendency for the parasite index in the villages sprayed with insecticide to be lower than that in the unsprayed villages.

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[1] *Chron. World Hlth Org.* 1950, **4**, 153

[2] *Chron. World Hlth Org.* 1949, **3**, 135

Pakistan

Following disinsection campaigns in Iswarganj Thana, Pakistan, the malaria control demonstration team [3] was able to compute in February 1950 that the parasite index among children under ten years of age was 6.2% in the sprayed area, whereas in the untreated comparison area it was 16.3%. The difference was especially marked in the age-group under two years, in which the parasite index was 7.1% in the sprayed zone and 37.5% in the unsprayed area.

Public Health in Lebanon

Dr J. M. Vine, adviser in public-health administration, visited Lebanon at the request of the Minister of Health of that country. With Dr F. W. Clements, Chief, WHO Nutrition Section, he had an opportunity to examine about one thousand children in the Palestine Arab refugee camps.

The possibilities of establishing a school of hygiene in Lebanon were considered. This school would train public-health officers, sanitary inspectors, and visiting nurses.

Yaws Control in Indonesia

Dr K. R. Hill, Professor of Pathology at the University College of the West Indies, Jamaica, has left Geneva for the Republic of Indonesia, where he will direct a yaws-control campaign which is being undertaken jointly by UNICEF and WHO.

From 1943 to 1945, Dr Hill took part in a campaign in West Africa for the control of yaws by the use of penicillin. He directed a team carrying out medical research on the Gold Coast on tropical diseases, including yaws and syphilis.

In Indonesia, Dr Hill will act as adviser on modern methods of yaws control as the medical officer in charge of a team which also includes a senior bacteriologist and a public-health nurse. Dr T. B. Turner, of the Research Laboratory, Johns Hopkins University, Baltimore, Md. — which is a WHO reference laboratory — will assist in the campaign from the USA. Strains from yaws and syphilis infections will be sent to him from Indonesia from comparative investigations of treponema strains from various parts of the world.

Czechoslovakia Decides to Withdraw from WHO

Mr V. Široký, Vice-President of the Council of Ministers and Minister for Foreign Affairs of Czechoslovakia, has given notice of the decision of his government to withdraw from WHO. His letter, addressed to the Director-General and dated 14 April 1950, states : " In the opinion of the Government of Czechoslovakia, the World Health Organization does not fulfil the aims and principles of its Constitution . . . The fundamental provisions of the Constitution of the World Health Organization have remained nothing but abstract watchwords. Moreover, the Organization is subject to political influences, leading even to discrimination against certain States Members, including Czechoslovakia. Developments within the World Health Organization are thus in contradiction with the principles of the Constitution, which were the preliminary condition for Czechoslovak participation ".

Czechoslovakia, since 1947, received assistance which included WHO participation in various national campaigns against tuberculosis and venereal diseases. A penicillin plant, donated by UNRRA, is now functioning satisfactorily, due, in part, to technical assistance given by WHO. Sixty-two fellowships have been granted to physicians from

[3] *Chron. World Hlth Org.* 1950, **4**, 153

the Czechoslovak health administration to enable them to study in other countries, including the USSR ; in 1950, $37,000 were allotted for the same purpose.

WHO assistance has also taken other forms, among which may be mentioned, in particular, the establishment of a State medical library and documentation centre at Prague ; WHO has already equipped a laboratory for microphotography, and has presented a considerable number of medical textbooks and monographs and subscriptions to 161 medical journals. In addition, an anaesthesiology training-centre was being organized at Prague with WHO aid ; international courses in modern techniques of anaesthesiology were to be given there. Finally, WHO planned to furnish all the medical and surgical equipment for a teaching centre devoted to congenital heart diseases. Arrangements had already been made for a group of Swedish specialists to go to Czechoslovakia in June to demonstrate new operative methods.

Government of Republic of China in Formosa Withdraws from WHO

A cable dated 5 May 1950 informed Dr Brock Chisholm, WHO Director-General, that China was withdrawing from the Organization as of 7 May and would not be represented in any organs of WHO, including the Third Health Assembly. The Chinese Government wished it to be known, however, that it would continue to adhere to the purposes and principles of WHO and to co-operate to the fullest possible extent in health matters with the Organization as a whole and with its Member States.

The communication came from Taipeh, Formosa, and was signed by George K. C. Yeh, Minister of Foreign Affairs, Republic of China.

Cambodia and Laos Request Membership

Cambodia and Laos have, on the 3 and 7 April respectively, submitted applications for membership to the World Health Organization. These applications were examined by the Third Health Assembly, which admitted these States to membership.

Seventy Member States of WHO

Nicaragua and Cuba have recently ratified the Constitution of WHO, thus bringing the total number of Member States of the Organization to 70. Names of countries which are now members of WHO may be found in *Chron. World Hlth Org.* 1949, **3**, 298 and 1950, **4**, 32.

CORRIGENDUM

1950, Vol. 4, No. 3, page 83

In the article entitled " Prevalence of plague in recent years ", the Azores were listed among the areas in Africa in which plague is prevalent.

The Department of Health, Ministry of the Interior, Lisbon, Portugal, has asked us to publish a corrigendum explaining that the Azores archipelago constitutes a part of continental Portuguese territory in Europe.